Modelling schizophrenia using human induced pluripotent stem cells.

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Public Summary:
Schizophrenia is a debilitating psychiatric disorder that affects approximately 1% of people worldwide. Previous studies have shown that patients with schizophrenia have reduced brain volume, smaller neurons and abnormal brain dopaminergic activity; however, the mechanism of disease initiation and progression remains unclear. To investigate these questions, we developed a new method to generate live human brain cells for the study of schizophrenia. Specifically, we reprogrammed skin samples from patients with schizophrenia into stem cells and then differentiated these stem cells into brain cells. Brain cells from patients with schizophrenia were less connected to each other and also showed specific differences in gene expression; some of these defects were improved by treatment with antipsychotic medications. Our findings are consistent with previous studies of schizophrenia, validating that it is now possible to study schizophrenia using live human brain cells generated through our methods.

Scientific Abstract:
Schizophrenia (SCZD) is a debilitating neurological disorder with a world-wide prevalence of 1%; there is a strong genetic component, with an estimated heritability of 80-85%. Although post-mortem studies have revealed reduced brain volume, cell size, spine density and abnormal neural distribution in the prefrontal cortex and hippocampus of SCZD brain tissue and neuropharmacological studies have implicated dopaminergic, glutamatergic and GABAergic activity in SCZD, the cell types affected in SCZD and the molecular mechanisms underlying the disease state remain unclear. To elucidate the cellular and molecular defects of SCZD, we directly reprogrammed fibroblasts from SCZD patients into human induced pluripotent stem cells (hiPSCs) and subsequently differentiated these disorder-specific hiPSCs into neurons (Supplementary Fig. 1). SCZD hiPSC neurons showed diminished neuronal connectivity in conjunction with decreased neurite number, PSD95-protein levels and glutamate receptor expression. Gene expression profiles of SCZD hiPSC neurons identified altered expression of many components of the cyclic AMP and WNT signalling pathways. Key cellular and molecular elements of the SCZD phenotype were ameliorated following treatment of SCZD hiPSC neurons with the antipsychotic loxapine. To date, hiPSC neuronal pathology has only been demonstrated in diseases characterized by both the loss of function of a single gene product and rapid disease progression in early childhood. We now report hiPSC neuronal phenotypes and gene expression changes associated with SCZD, a complex genetic psychiatric disorder.